IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

PERNIX IRELAND PAIN DAC and PERNIX THERAPEUTICS, LLC,	)	
Plaintiffs,	)	C.A. No. 16-139-WCB
v.	)	[redacted]
ALVOGEN MALTA OPERATIONS LTD.,	)	
Defendant.	)	PUBLIC VERSION FILED: April 24, 2018

PLAINTIFFS' REPLY IN SUPPORT OF THEIR MOTION
FOR SUMMARY JUDGMENT OF NO INVALIDITY UNDER 35 U.S.C. § 101

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Cases

Alvogen's arguments in opposition to Pernix's motion for summary judgment of no invalidity under § 101 are without merit. First, Alvogen argues the claims are not "directed to" a method of treatment, even though they plainly recite a method of treatment. Alvogen's argument is undermined by its previous admission that the claims are in fact "directed to a method of treat[ment]." Regardless, Alvogen's theory sets an unworkable standard that turns not on the language of the claims, but on an infringer's arbitrary characterization of their "focus." Second, Alvogen dismisses as dicta the guidance in *Mayo* and *CellzDirect* on method of treatment claims. But the Federal Circuit's precedential opinion in *Vanda*, issued last week, followed that "dicta" and held that method of treatment claims are **not** directed to a natural law. Third, Alvogen disregards the Court's *Markman* decision because the Court did not explicitly adjudicate subject matter eligibility. But Alvogen provides no reason for overturning the Court's findings that the claimed methods differ from conventional methods.

I. The claims are directed to a method of treatment.

Alvogen asserts that the claims-at-issue—contrary to their express language—are not "directed to" a method of treatment because that limitation is not the "alleged advance relative to the prior art." D.I. 145 at 3, 6. First, Alvogen ignores that the claims set forth a simpler method of treating pain that overcomes problems in the prior art, such as the risk of inadequate pain relief when administering a lower starting dose to hepatically impaired patients. D.I. 116 at 2-5. Second, Alvogen's focus on individual limitations and whether they are present or absent in the prior art conflates subject matter eligibility and novelty. *McRO, Inc. v. Bandai Namco Games Am. Inc.*, 837 F.3d 1299, 1312 (Fed. Cir. 2016) (under *Alice* step one, "the claims are considered **in their entirety** to ascertain whether their character **as a whole** is directed to excluded subject matter."); *Diamond v. Diehr*, 450 U.S. 175, 188-90 (1981) ("The 'novelty' of any element or steps in a process, or even of the process itself, is of **no relevance** in determining whether the

subject matter of a claim falls within the § 101 categories of possibly patentable subject matter"; "whether a[n] invention is novel is **wholly apart** from whether the invention falls into [the § 101] categor[ies]."). [1] Third, contradicting its § 101 position here, Alvogen contends in its interrogatory responses that "each of the claims of the Asserted Patents is **directed to a method of treating** patients . . ." Ex. A at 8. [2] Alvogen's flip-flop is a futile attempt to avoid the Federal Circuit's analysis in *Rapid Lit. Mgt. Ltd. v. CellzDirect, Inc.*, 827 F.3d 1042, 1048-49 (Fed. Cir. 2016), where it found eligible claims that, "like thousands of others [*e.g.*, 'methods of treating disease'], recite processes to achieve a desired outcome." Here, Alvogen does exactly what the Federal Circuit cautioned against. *Compare* D.I. 145 at 13 (the asserted claims "are directed to a natural law" because "their focus is the body's metabolism of [HC-ER] formulations.") *with id.* ("That one way of describing the process is to describe the natural ability of the subject matter to undergo the process does not make the claim 'directed to' that natural ability.")

Alvogen also notes that "the method of treatment limitation appears in the preamble, which is presumptively non-limiting" (D.I. 145 at 6 n.4), though Alvogen cites no authority for ignoring a preamble under § 101. And, unlike the starting dose limitation, Alvogen did not argue during claim construction proceedings that the preamble is not limiting. To the contrary, Alvogen has repeatedly relied on the preamble as a limitation throughout this litigation. Ex. A at 6-7; Ex. B at A-22 ("Alvogen does not and will not directly infringe any claim of the '499 patent because each claim relates to a method of treatment . . . . Alvogen, however, does not treat patients."). Thus, Alvogen has waived any argument that the preamble is non-limiting.

Regardless, the preamble limits the claims because it provides antecedent basis for "the

[1] That removing claim terms would render other limitations "mere empty language" (D.I. 145 at 1, 3, 6, 18) requires, rather than weighs against, considering all of the limitations as a whole.

[2] Unless otherwise indicated: "Ex." refers to an exhibit attached to the Declaration of Josh Calabro, Esq.; emphases have been added; and objections have been omitted.

patient" recited in the body the claims. *See Rapoport v. Dement*, 254 F.3d 1053, 1059 (Fed. Cir. 2001) (preamble "method for treatment of sleep apneas" limiting because it provided antecedent basis); *Blue Calypso, Inc. v. Groupon, Inc.*, 93 F. Supp. 3d 575, 594 (E.D. Tex. 2015). In addition, the "method of treating pain" provides antecedent basis for the "treatment" in the body of the claims, as construed by the Court. D.I. 69 at 2. Moreover, treating pain is "underscored as important" by the title and specification of the patents-in-suit. D.I. 116 at 2-5; *Rotatable Techs. LLC v. Motorola Mob. LLC*, 567 F. App'x 942, 943 (Fed. Cir. 2014); *Purdue Pharm. Prods. v. Actavis Eli., LLC*, No. 12-cv-5311, 2014 U.S. Dist. LEXIS 80920, at *24-25 (D.N.J. June 11, 2014) (preamble "a solid unit dosage composition for the treatment of MOTN insomnia" limiting because it gave life and meaning to claims), *aff'd*, 627 F. App'x 931 (Fed. Cir. 2016).

II. The Federal Circuit confirmed that methods of treatment are patent-eligible.

In *Vanda Pharm. v. West-Ward Pharm. Int'l*, Nos. 2016-2707, -08, 2018 U.S. App. LEXIS 9360 (Fed. Cir. Apr. 13, 2018), the Court found that claims to a method of treating schizophrenia with iloperidone that is safer for patients because it reduces the risk of QTc prolongation by requiring a lower dose for CYP2D6-poor metabolizers are eligible under § 101. And, the Court found unpersuasive nearly all of Alvogen's theories here.

First, Alvogen argues the claims are ineligible because they are "**premised upon** [a] natural law"—"**the relationship** between the bioavailability of certain hydrocodone ER dosage forms and patients with HI."[3] D.I. 145 at 5, 8-9 ("That a claim may happen to recite a method of treatment does not change the result under the Step One 'directed to' standard."). *See Vanda*, 2018 U.S. App. LEXIS 9360, at *39 (claims eligible under step one because "[t]hey recite more than the natural relationship between CYP2D6 metabolizer genotype and the risk of QTc

[3] The asserted claims are not even based on a natural law, as discussed below in Section IV.

prolongation," *i.e.*, "a **method of treating patients based on this relationship**.").

Second, Alvogen argues "the Asserted Claims do not even cover a new way of using an existing drug," but rather "cover using hydrocodone to treat a condition (pain) that it was already known to treat." D.I. 145 at 8. *See Vanda*, 2018 U.S. App. LEXIS 9360, at *36 (The "claims are 'a new way of using an existing drug,'" notwithstanding that they cover using iloperidone to treat a condition (schizophrenia) that it was already known to treat), quoting *Mayo*, 566 U.S. at 87.[4]

Third, Alvogen argues that "no legal authority" supports Pernix's contention "that the Asserted Claims are not directed to a natural law because they recite 'applications' that implement the law as opposed to mere 'observations.'" D.I. 145 at 14. *See Vanda*, 2018 U.S. App. LEXIS 9360, at *35-36 ("The inventors recognized the relationships between iloperidone, CYP2D6 metabolism, and QTc prolongation, but that is not what they claimed. They claimed an application of that relationship."); *see* D.I. 116 at 10.

Fourth, Alvogen argues the "specifications expressly characterize the 'basic concept' of the alleged invention as the observation of" the PK results in Fig. 6. D.I. 145 at 5. *See Vanda*, 2018 U.S. App. LEXIS 9360, at *50 (Prost, J., dissenting) ("The '610 patent itself identifies its invention as 'compris[ing] the discovery that treatment of a patient, who has lower CYP2D6 activity than a normal person, with a drug that is pre-disposed to cause QT prolongation and is metabolized by the CYP2D6 enzyme, can be accomplish[ed] more safely by administering a lower dose of the drug.'")

Fifth, Alvogen argues that in "*Mayo*, the Supreme Court held that claims reciting

[4] The background section of the patent at-issue in *Vanda* admits it was known: (1) to treat schizophrenia with iloperidone; (2) the CYP2D6 gene encodes an enzyme that metabolizes iloperidone; and (3) "increased concentration of iloperidone or its metabolites" was linked to prolongation of the QT interval. Ex. C at 49-50, citing Ex. D at 1:29-61, 4:24-25. So the claims related to a "known side effect of an existing treatment." 2018 U.S. App. LEXIS 9360, at *55.

administration of an active drug **to treat** patients with gastrointestinal disorders was patent ineligible." D.I. 145 at 7. *See Vanda*, 2018 U.S. App. LEXIS 9360, at *35, *37 ("Although the . . . claim in *Mayo* recited administering a thiopurine drug to a patient, the claim as a whole was **not** directed to the application of a drug **to treat** a particular disease. Instead, the claims were directed to a diagnostic method.").

Sixth, Alvogen argues that the "*Mayo* Court's statement regarding 'tying up a doctor's treatment subsequent decision' solely concerns the Court's determination that the *Mayo* claims preempted use of a natural law and is not part of the Step One inquiry." D.I. 145 at 9. *See Vanda*, 2018 U.S. App. LEXIS 9360, at *37-38 (claims eligible under step one because they "recite steps of carrying out a dosage regimen," *e.g.*, "internally administer[] iloperidone to the patient in an amount of 12 mg/day or less," and thus do not "tie up the doctor's subsequent treatment decision whether that treatment does, or does not, change in light of the inference he has drawn using the correlations," as in *Mayo*).[5]

Seventh, Alvogen argues that "FDA Guidance provides exactly when to [not adjust the dose] and the named inventors did nothing more than follow its teachings." D.I. 145 at 19. *See* Ex. C at 51 (defendant in *Vanda* arguing unsuccessfully that claims are ineligible because FDA "requires studies to determine the appropriate dose adjustments based on CYP2D6 status, which [were] conducted for iloperidone."); *see Vanda*, 203 F. Supp. 3d 412, 428 (D. Del. 2016).

Alvogen also misplaces reliance on non-binding *Endo* and *Boehringer* district court decisions. D.I. 145 at 7. First, both opinions issued before the Federal Circuit made clear in *Vanda* that method of treatment claims are patent-eligible. Second, the patentee in *Endo*

[5] The asserted claims' recitation of a relative rather than absolute dose is inconsequential; requiring PK profiles or no starting dose adjustment sets a specific treatment decision based on the inventors' unexpected discovery to the same extent that "12 mg/day or less" did in *Vanda*.

"concede[d] the first step of the *Mayo* analysis." 2015 U.S. Dist. LEXIS 127104, at *15, 2015 U.S. Dist. LEXIS 155034, at *3, *7. Contrary to Alvogen's alleged "undisputed" facts, Pernix never admitted that the non-adjustment limitation and PK profiles "recite and restate a natural law." D.I. 145 at 2. They do not. Rather, those limitations are a "new way of using an existing drug," which the Supreme Court deemed to be eligible subject matter. *Mayo*, 566 U.S. at 87.[6] Third, the claims in *Endo*, like those in *Mayo*, left the treatment decision unresolved, instructing physicians to "measur[e] a creatinine clearance" and then administer an unspecified "lower dosage," "in dependence on which creatinine clearance rate is found." 2015 U.S. Dist. LEXIS 127104, at *3-4. Those claims thus amounted to "informing the patient or prescribing physician that the bioavailability of oxymorphone is increased in patients with renal impairment." 2015 U.S. Dist. LEXIS 155034, at *7; 2015 U.S. Dist. LEXIS 127104, at *15; *see Mayo*, 566 U.S. at 67 (the claims "simply tell doctors to gather data from which they may draw an inference in light of the correlations," *i.e.*, "the claims inform a relevant audience about certain laws of nature"). The asserted claims, by contrast, do not merely "inform" an audience of a natural law; they require "delivering into the body" a specific dose of an ER hydrocodone oral dosage unit to treat pain. Fourth, the district court in *Boehringer* found that the claimed "instruction of administering the DPP-IV inhibitor to the targeted patient population . . . can be conducted via **mental processes**, which is not tied to any tangible embodiments." 2016 U.S. Dist. LEXIS

[6] It makes no difference that the Supreme Court did so in context of preemption (D.I. 145 at 8), as preemption is the "concern that undergirds . . . § 101 jurisprudence." *Alice Corp. Pty. Ltd. v. CLS Bank Int'l*, 134 S. Ct. 2347, 2358 (2014). And, Alvogen does not even try to reconcile its reliance on extrinsic evidence purporting to show that one element (6-thioguanine) of the claim in *Mayo* is non-naturally occurring—an issue never mentioned in the Supreme Court's opinion—with its position that the *Mayo* Court's express statement concerning "new way[s] of using an existing drug" is irrelevant. D.I. 145 at 12. Alvogen's theory that man-made compositions are not the "basis" of the asserted claims because Devane discloses ER hydrocodone formulations (*id.*at 13) also overlooks the Federal Circuit's holding in *Molecular Pathology* that man-made cells rendered claims eligible irrespective of "novelty or nonobviousness." D.I. 116 at 12.

169812, at *28, *32. In its *Markman* decision, the Court here found "having a patient ingest the same initial dose regardless of their hepatic impairment is **not just a mental step**," but instead affects how the physical steps are performed. D.I. 69 at 3 n.2. The Court further tied the claims to a tangible embodiment by construing "administering" to require "delivering into the body." *Id.* at 1. Fifth, the Court in *Boehringer* emphasized "the inventive concepts of the '156 patent not requiring dose adjustment is **not an issue in the cited claims** of infringement," and therefore could not confer patent-eligibility. *Id*. at *13-14. Here, the asserted claims expressly recite the inventive concept of no dose adjustment (or require a PK profile that enables such dosing).

Alvogen's reliance on the PTO guidance undermines its argument. The PTO found claim 5 directed to a natural law because it recites "diagnosing the patient with julitis when the presence of JUL-1 in the plasma sample is detected." D.I. 117-1, Ex. E at 10. The asserted claims contain no such diagnosing limitation. The "method of treating" limitation in the asserted claims tracks verbatim the "method of treating" limitation in PTO's claim 7, which the PTO found **not** directed to a natural law, and lacks the element of claim 5's "method of **diagnosing** and treating" that led to a different conclusion. In any event, the PTO found claim 5 eligible.

III. The Court's *Markman* findings are law of the case and applicable to *Alice* step two.

Alvogen admits that claim constructions are law of the case and cites no authority that findings underlying a *Markman* decision are not law of the case. D.I. 145 at 21-22.[7] Alvogen tries to dismiss as "dicta" the Court's finding that the starting dose limitation is a "manipulative difference over the prior art." D.I. 145 at 22-23. But in addressing Alvogen's argument under the *BMS* case, the Court had to analyze conventional methods to determine whether the starting

[7] Alvogen misplaces reliance on *Toro Co. v. White Consol. Indus., Inc.*, 383 F.3d 1326, 1336-37 (Fed. Cir. 2004), where the Court found a claim construction insufficient to invoke the disclosure-dedication rule, but ultimately refused to "disregard[] the law of the case."

dose term limits the claims (D.I. 116 at 15-16), which is the same analysis as *Alice* step two. Even Alvogen's case law makes clear that *BMS* requires the same inquiry as *Alice* step two. *Compare Aventis Pharms. v. Barr Labs.*, 411 F. Supp. 2d 490, 523 (D.N.J. 2006) ("In *BMS*, the court construed a claim's preamble . . . [by] comparing the process of the invention with that in the prior art, . . . and **look[ing] for an identity of physical steps**.") *with Genetic Techs. Ltd. v. Merial LLC*, 818 F.3d 1369, 1377 (Fed. Cir. 2016) (under *Alice* step two, looked at "the **physical steps** by which claim 1 implements the natural law . . . to determine whether they provide more than 'well-understood, routine, conventional activity' already engaged in by those in the field").[8]

Alvogen further concedes that "[t]he law of the case doctrine [applies] to issues that were actually decided, either explicitly or by necessary **implication**." D.I. 145 at 20-21, quoting *Toro*, 383 F.3d at 1335. Judge Sleet decided, by necessary implication, that the claims contain an inventive concept. D.I. 69 at 3 n.2 (starting dose limitation affects "how the administering step is performed . . . because patients with hepatic impairment ingest a different dose than they normally would, given the prior art."). Alvogen alleges the Court did not consider "every conceivable piece of prior art" in its *Markman* decision. D.I. 145 at 21. But "[p]atent eligibility has in many cases been resolved on motions to dismiss," when Courts cannot consider all of the prior art. *Berkheimer v. HP Inc.*, 881 F.3d 1360, 1368 (Fed. Cir. 2018). In any event, Judge Sleet rendered that decision knowing the claims contain "no **compositional** difference over the prior art" in view of the Devane reference that Alvogen relies on in its § 101 opposition. D.I. 69 at 3 n.2.

[8] Alvogen incorrectly asserts "Pernix fails to acknowledge this binding legal precedent . . . of *Genetic Techs.* and *Ariosa*." D.I. 145 at 18. Pernix cited both cases in its opening brief. D.I. 116 at 15.

The four pages Alvogen spends arguing that a natural law cannot furnish an inventive concept (D.I. 145 at 16-19) are irrelevant in view of the Federal Circuit's confirmation in *Vanda* that methods of treatment are not natural laws. Here too, Alvogen improperly strips away claim limitations and fails to address the claimed method of treatment as a whole. *Compare* D.I. 23 at 18 ("All limitations of the Asserted Claims outside the [starting dose limitation] provide well-understood, routine and conventional activity.") *with CellzDirect*, 827 F.3d at 1051 (Fed. Cir. 2016) ("[I]n examining claims under step two, we must view them **as a whole**, considering their elements 'both individually and '**as an ordered combination**.'").

IV. The asserted claims do not preempt any natural law.

Alvogen defines the "natural law here [as] the relationship between HI and the bioavailability of hydrocodone in the body after administration of **certain** hydrocodone ER formulations" (D.I. 145 at 24). No such law exists. Only "certain" hydrocodone ER formulations produce the claimed PK profile that enables no adjustment of the starting dose, thus no universal law of nature governs "the relationship between HI and the bioavailability of hydrocodone in the body." *Id.* Alvogen's circular preemption argument—that "[t]he Asserted Claims **preempt that natural law** by precluding administration of any and all hydrocodone-only ER formulations **that satisfy the natural law** in HI patients"—therefore fails. *Id.*; *see* D.I. 116 at 18-19. Alvogen also asserts the claims "preempt all uses of all HC-ER formulations that to [sic] satisfy the PK limitations and non-adjustment limitation." *Id.* at 25. But the claims are limited to treating pain in particular patients. And, claims are not rendered ineligible because they preempt use of the inventors' invention.

* * * *

For the foregoing reasons, the Court should grant Pernix's motion.

Respectfully submitted,

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April 17, 2018

CERTIFICATE OF SERVICE

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